

Frankincense (*Boswellia* Species): The Novel Phytotherapy for Drug Targeting in Cancer

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Abstract

It seems that frankincense might have a potential ability to be used as an alternative natural medicine not only for cancer, chronic and inflammatory diseases but also for the patients with brain and memory disorders. Frankincense, the resinous extract from the trees of the genus *Boswellia*, has been used for centuries in ceremonial, cosmetic, cultural and as a traditional medicine to treat a variety of ailments especially cancer, inflammatory diseases including asthma, arthritis, cerebral edema, chronic pain syndrome, chronic bowel diseases, and some other illnesses. Boswellic acids are the active compounds of frankincense and AKBA (3-O-acetyl-11-keto- β -boswellic acid) is the most important and effective acid among them. Some studies have shown that the use of frankincense can also improve the learning and enhance the memory in animals and human.

Keywords: *Boswellia* species, Anti-inflammatory, Chronic diseases, Cancer, Memory enhancement

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Introduction

Frankincense is a French word, meaning "pure incense". It is popularly known as Indian olibanum, Salai guggal, Loban, or Kundur. It has been used as an incense and fumigating preparation for religious rituals, in cultural ceremonies and as a traditional remedy for treating various diseases [1]. The oleogum resins are secreted by trees of the *Boswellia* species which are tropical, deciduous trees and usually grow as small trees or shrubs with the limited natural growing range [2]. The growing of the trees has been extended by cultivation to meet the worldwide demand [3]. The resin is obtained by making scrapes in the trunk of the various *Boswellia* species (Burseraceae), and later collecting the dried resin gums from the trees [2,4]. The good quality of resin is produced only for three years and after this period, the quality of collected resin decreases significantly, then the tree should be left to rest for some years after the harvesting period [5].

Olibanum is produced mainly by four species from different regions such as *Boswellia serrata* from India, *Boswellia carterii* from East Africa and China, *Boswellia frereana* from Northeast Africa (Somalia) and *Boswellia sacra* from Middle East [6,7]. Today the most traded frankincense is produced in Oman, Yemen and Somalia [3].

Since ancient times, Frankincense has been used in many

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countries such as Africa, China, India and Middle East countries for the prevention and treatment of various illnesses especially chronic inflammatory diseases [2,8]. In Indian system of medicine, Frankincense (salai guggal) has been used as an anti-inflammatory, anti-arthritic, anti-proliferative and analgesic agent for the treatment of related diseases [9]. In Traditional Chinese Medicine (TCM), frankincense of *Boswellia carterii* is commonly used as a remedy for improving blood circulation and as relieving pain in leprosy, gonorrhoea and cancer patients [10].

In the last decade, the use of olibanum has become more popular in European countries for the treatment of variety of chronic inflammatory problems such as arthritis, chronic bowel diseases, asthma, peritumoral brain edema and other diseases [11].

The mechanism of anti-inflammatory activity of the *Boswellia*

extract is due to the boswellic acids which are the active principals of frankincense. The chemical structure of boswellic acids closely resembles steroids [9], which their actions are different than painkillers or NSAID (non-steroid anti-inflammatory drug) and is related to the component of the immune system and the inhibition of 5-lipoxygenase [11].

Composition

There are many different compounds found in a variety of *Boswellia* species [11]. The composition of the essential oil and other contents changes from species to species, and differs depending on the climate, harvest conditions and geographical locations [11,12].

Frankincense is reported to contain 60-85% resins (mixtures of terpenes), 6-30% gums (mixture of polysaccharides) and 5-9% essential oil [13]. Resin portion is composed of pentacyclic triterpenes which boswellic acid is the active functional group [14]. Gum portion is consisting of pentose and hexose sugar with some oxidizing and digestive enzymes. The essential oil is the mixture of monoterpenes, diterpenes and sesquiterpenes [14].

In a study was reported that the resinous part of *Boswellia serrata* contains terpenes: monoterpenes (α -thujone); diterpenes (macrocyclic diterpenoids such as incensole, incensole oxide, iso-incensole oxide, a diterpene alcohol [serratalol]); triterpenes (such as α - and β -amyrins); pentacyclic triterpenic acids (boswellic acids); tetracyclic triterpenic acids (tirucall-8, 24-dien-21-oic acids) [5].

Boswellic acids with the molecular formulas of C₃₂ H₅₂ O₄ are the main active component of frankincense [12]. The four major boswellic acids (pentacyclic triterpenic acids) found in frankincense are: β -boswellic acid (BA), acetyl- β -boswellic acid (ABA), 11-keto- β -boswellic (KBA) acid and 3-O-acetyl-11-keto- β -boswellic acid (AKBA) which they have shown to be responsible for the inhibition of Pro-inflammatory enzymes [5]. Among these four boswellic acids, acetyl-11-keto- β boswellic acid (AKBA) is the most important inhibitor of an enzyme called 5-lipoxygenase which is responsible for inflammation [5]. AKBA has shown to be effective against a large number of inflammatory diseases such as arthritis, bronchial asthma, chronic colitis, ulcerative colitis, Crohn's disease and cancer [15]. The mechanism of the action is due to the binding of AKBA to 5-lipoxygenase in a calcium-dependent and reversible and act as a non-redox type, non-competitive inhibitor [16-25] (Figure 1).

Cancer

Plants are rich sources of antitumor compounds. Oleogum resins from various *Boswellia* species contain triterpenoids with antitumor properties [26]. In a report, the anti tumor activities of the four triterpenic acids (BA, ABA, KBA and AKBA) isolated from the gum resin of *Boswellia serrata* were studied and it was found that these acids inhibited the synthesis of DNA, RNA and protein in human leukemia HL-60 cells in a dose dependent system. Among them AKBA induced the most pronounced inhibitory effect on DNA, RNA and protein synthesis in which the effect on DNA synthesis was found to be irreversible. This compound significantly inhibited the cellular growth of HL-60 cells, but did

not affect cell viability [24].

The studies have shown that boswellic acids are potent apoptotic agents to cancer cells. The boswellic acid acetate seems to induce apoptosis in six human myeloid leukemia cell lines through a Caspase-mediated pathway which is activated by the induction of the death receptors 4 and 5 (DR4, DR5) [27]. The anticancer activity of AKBA is attributed to the inhibitory effect on the lipoxygenases leading to the inhibition of cell proliferation and induction of apoptosis in tumor cells [15].

Prostate cancer

It has been shown in several studies that pentacyclic triterpenoids found in *Boswellia serrata* have inhibitory effect on the growth of prostate cancer cells [26]. Among boswellic acids, Acetyl-11-keto- β -boswellic acid (AKBA) has special inhibitory effect in prostate cancer by suppressing vascular endothelial growth factor receptor 2-mediated angiogenesis [5]. Also tirucallic acids isolated from the oleogum resin of *Boswellia carterii* work as an effective Akt inhibitors which apply cytotoxic effects in human prostate cancer cell lines *in vitro* and *in vivo* [26].

Akt is a serine/threonine protein kinase which has an important role in multiple cellular processes such as cell proliferation, apoptosis, transcription and cell migration. Akt1 has been associated as a major factor in many types of cancer since it can block apoptosis and promote the survival of the cell [26].

Brain tumor

Brain cancer is a condition in which malignant tumors develop within the brain. These tumors are fast growing and invade surrounding tissues. The surgical removal of brain tumors is a hard and detailed procedure and in many cases the complete removal of the tumor is not possible because of the size, type and location of the tumor. For these reasons, the average survival of brain tumor patients is only about nine months even after the treatment of surgery and radiotherapy are combined [28]. In addition the use of chemotherapy is able to prolong the survival of only about 10% of the patients [28]. In patients with malignant brain tumors, highly active forms of leukotrienes and other inflammatory mediators are produced in the brain and around tumors, causing localized fluid build-ups and damages to the healthy nerve cells [29].

The impact of *Boswellia serrata*, with its anti-inflammatory effect has been studied in patients with brain tumors [29]. An ethanolic extract from the gum resin of *Boswellia serrata* contains the boswellic acids which the study have shown after the application of this preparation which is called phytopharmakon H15 for the period of seven days a reduction of the peritumoural brain edema of 22 to 48% was observed. In contrast to the cells of untreated patients, the cells of the treated tumor tissue show no tendency to proliferate within two weeks [28].

The report on patients with malignant glioma showed that the use of 3600 mg/day of *Boswellia* extract (60% boswellic acids), seven days prior to surgery caused decrease of the fluid around the

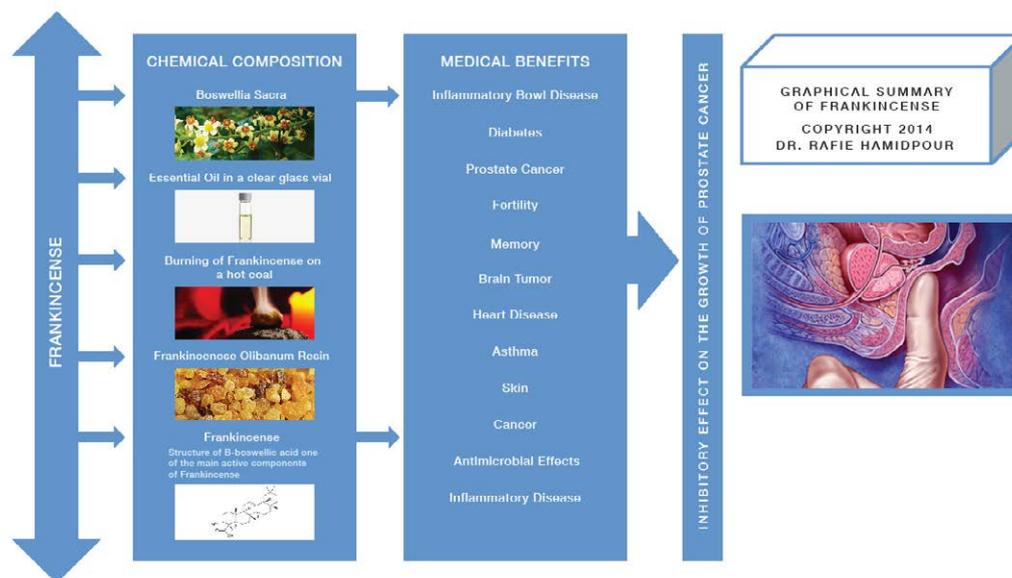


Figure 1 Graphical Summary of Frankincense.

tumor with average of 30% in 8 of the 12 patients and the signs of brain damage decreased during the treatment [29]. Recently the detailed study in patients with malignant cerebral tumors who were receiving radiotherapy plus certain amount of *Boswellia* extract, showed that after the end of radiotherapy the 75% reduction of cerebral edema was observed in 60% of the patients receiving *Boswellia* extract. The study also shows the ratio of tumor over volume decreased in these patients, suggesting anti-tumor effect in addition to the anti-edema activity [29].

Controlled release of drugs

Controlled released drug delivery systems are intended to direct the delivery of the drugs to targeted tissues, in desirable and sustaining rates. Among a variety of approaches, preparation of drug-embedded matrix tablets is widely used for this purpose [30]. Although a wide variety of polymers are used in matrix tablets for controlling the drug delivery or improving the bioavailability of the contained drug, the need for safe, natural and effective matrix tablets has always existed.

The use of olibanum resin is considered suitable for the controlled release of diclofenac over 24 hr. (once a day administration) [30]. Also in a study on the control release of nifedipine, olibanum and colophony, two natural resins were used as a microencapsulation agents which caused the slow and spread release of the drug over 24 hour [31].

Olibanum resin is a natural lipophilic polymer which is used as a microencapsulating agent for the good controlled release of the drugs [32]. The result of studies on the matrix tablets formulated with the use of olibanum resin in several drugs like diclofenac, nifedipine, carbamazepine have shown that as the concentration of olibanum resin in the matrix tablets increased the drug release was decreased [30], which this means the longer stay of drug in the body [31].

Preparation and dosages

Although different methods of preparations can be formulated for oral, rectal and parenteral administration, the preparations of oral administration are preferred. The pharmaceutical preparations for oral administration may be in the form of tablets or capsules prepared with the use of diluents, such as binding agents, fillers, lubricants, disintegration agents or wetting agents [28].

The compounds can also be formulated for injection, preferably intravenous, intra-arterial, intramuscular, intracranial, intrathecal or subcutaneous and can be in unit dosage form, e.g. in ampoules, or in multiple dose containers with the preservative added. The preparations may be in the form of suspensions, solutions, or emulsions in oily or aqueous carriers [28].

Boswellia is generally taken orally as a capsule, tablet or its bark decoction. The standardization of *Boswellia* products is difficult because of variety of *Boswellia* products [5]. The suggested dosages for inflammatory or asthmatic conditions are 300 to 400 mg of standardized extract (containing 60% boswellic acids) three times daily [5].

Safety

Frankincense, the gum resin of *Boswellia*, which has been used as a remedy for more than thousands of years has not shown any severe side effects and is considered to be safe [25]. The anti-inflammatory effects of *Boswellia* unlike of many anti-inflammatory chemical drugs, dose not cause any adverse effects on blood pressure, heart rate, respiration or other autonomic responses with remarkably low toxicity [17]. Gum resin of *Boswellia* is included in the list of safe substances and its use is permitted by USFDA as a food additive [15].

Oral preparations of boswellic serrata extract containing AKBA

are sold in the market over the counter as anti-inflammatory formulations [15]. The results of many clinical studies have shown that *Boswellia* is well tolerated in the treatment of rheumatoid arthritis and Crohn's disease with minimum side effects [29].

Taken together, the side effects of Frankincense, is relatively very low and not severe when compared to modern drugs and their side effects. Then they can be considered quiet safe when are

taken in the required and therapeutic dosages.

Conclusion

Frankincense has been used in traditional and modern natural medicine for the treatment of variety of illnesses with very minimal side effects. The anti-inflammatory, anti-arthritis, anti-proliferative, anti-microbial and analgesic effect of this gum resin

can reduce the inflammation and pain in the body and relieve the related symptoms of many diseases. The effect of frankincense is remarkable in increasing the number of dendritic segments and branching in the neuron cells of hippocampus, causing more synaptic connections in that area and therefore improvement of learning and memory. Extensive studies on frankincense and its effect on neurophysiology could be a right approach in finding a possible new complementary or alternative natural medicine to control, cure or prevent some variety of neurodegenerative diseases such as Parkinson's and Alzheimer's diseases.

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